60. (New) The method of claim 33, wherein the complex of the pharmaceutical composition comprises a fusion protein.

61. (New) The method of claim 33, wherein the complex of the pharmaceutical composition is derived from a tumor.

62. (New) The method of claim 33, wherein the hsp110 of the pharmaceutical composition is complexed with hsp70 and hsp25.

63. (New) The method of claim 33, wherein the immunogenic polypeptide of the pharmaceutical composition comprises a her-2/neu peptide.

64. (New) The method of claim 63, wherein the her-2/neu peptide is derived from the intracellular domain of her-2/neu.

65. (New) The method of claim 63, wherein the her-2/neu peptide is derived from the extracellular domain of her-2/neu.

66. (New) The method of claim 63, wherein the her-2/neu peptide is derived from the transmembrane region of her-2/neu.

67. (New) The method of claim 33, wherein the cancer is colon cancer.

68. (New) The method of claim 33, wherein the complex of the pharmaceutical composition has been heated so as to enhance binding of the hsp110 polypeptide to the immunogenic polypeptide.

69. (New) The method of claim 33, wherein the pharmaceutical composition further comprises an adjuvant.

REMARKS

I. Introduction

In response to the Office Action dated July 9, 2002, claims 11-15, 24-32 and 35-45 have been cancelled, claims 1-3, 9, 16, 19-22, 33 and 34 have been amended, and new claims 46-69 have

been added. Claims 1-10, 16-23, 33, 34 and 46-69 remain in the application. Reconsideration of the application, as amended, is respectfully requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required for patentability or to distinguish the claims over the prior art.

Applicants note that the amendment to claims 1-3, 9 and 22 to delete reference to "or grp170" was made solely to conform to the restriction requirement and, by removing an element, does not narrow the scope of these claims.

The amendment to claim 16 merely restates that the immunogenic polypeptide "associated with a cancer" comprises a "cancer antigen". Because these are merely alternative statements of what is widely understood in the art, that a polypeptide associated with a cancer is a cancer antigen, this amendment does not narrow the scope of claim 16.

Claims 19 and 20 were amended to delete reference to non-elected subject matter and replace it with language that is supported by the specification at page 25, line 29, and also falls within the elected subject matter.

Claim 21 was amended to delete reference to non-elected subject matter and replace it with language that is supported throughout the Examples provided in the specification, such as at page 48, line 24, and also falls within the elected subject matter.

Claims 33 and 34 were amended to clarify that the "effective amount" recited in the claims as originally filed refers to the originally recited function of "inhibiting tumor growth" or "inhibiting the development of a cancer". Accordingly, this amendment does not narrow the scope of these claims.

New claims 46-49 and 58-61 are supported by originally-filed claims 2-5. New claims 50 and 62 are supported by originally-filed claim 8. New claims 51-52 and 63-64 are supported by originally-filed claims 17 and 18. New claims 53-54 and 65-66 are supported by the specification at page 25, line 29. New claims 55 and 67 the specification at page 48, line 24. New claims 56-57 and 68-69 are supported by originally-filed claims 22-23.

These amendments to the claims are therefore supported by the application as originally filed, and entry of these amendments is respectfully requested.

III. Restriction Requirement

Applicants acknowledge that the Examiner has made the restriction requirement final. Claims directed to non-elected subject matter have been canceled.

IV. Claim Objections

In paragraph (5) of the Office Action, claims 1-10, 16-18, 22, 23, 33 and 34 were objected to because claims 1-3, 9 and 22 recite a reference to a non-elected invention. Applicants have amended claims 1-3, 9 and 22 to correct this informality.

V. Non-Art Rejections

In paragraphs (6)-(7) of the Office Action, claims 7, 16, 33 and 34 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendments to claims 16, 33 and 34 render the rejection of these claims moot. Regarding claim 7, Applicants respectfully traverse this rejection for the reasons elaborated below.

A. Claim 7

Claim 7 was rejected because the recitation of "members of the hsp70, hsp90, grp78 and grp94 stress protein families" was regarded as rendering the claim vague and indefinite because it is unclear to which proteins the claim refers, as it is allegedly unclear which proteins are members of the hsp70, hsp90, grp78 and grp94 families. As described in the specification at page 2, lines 12-22, the various families of stress proteins are identified in accordance with their approximate molecular weights. Those of ordinary skill in the art are familiar with this system of categorization and with which stress proteins belong to which family. Consideration of the references cited by the Examiner confirms this familiarity within the art. For example, see: Przepiorka & Srivastava 1998 (see Table 1); Manjili et al. 2002 (see pre-filing date references cited in Part 3 therein); Li 1997 (see pages 315-316); Srivastava 1997 (see page 165); Blachere & Srivastava 1995 (see page 349); and Lee-Yoon 1995

(see Introduction and Discussion at pages 15725 and 15731-32). Accordingly, those skilled in the art have no difficulty ascertaining the metes and bounds of claim 7 as originally filed.

An additional concern is raised that the claim would encompass any member of the stress protein families that has yet to be discovered or categorized as such, which proteins could not have been contemplated by Applicants and which have not been adequately described in the specification. This latter concern does not relate to definiteness (see MPEP §2173.04), and also implies that no claim term is acceptable if it possibly encompasses compositions of matter identified in the future as falling within the claim term. Yet it is quite possible that additional cancers may be identified in the future, or perhaps additional adjuvants will be identified in the future. Applicants maintain that the existence of such an eventuality does not render all claims that recite common terms such as "cancer" or "adjuvant" indefinite.

Claim 7 relates to the synergistic benefits described in Applicants' specification (see Example 7 at pages 54-61, particularly the Discussion at pages 59-61) of combining hsp110 with additional stress proteins. This should be regarded as analogous to claim 23, which recites "further comprising an adjuvant". Whether every possible adjuvant now known or to be identified in the future is explicitly recited in the specification is not relevant to the definiteness of claim 23, nor is such a recitation required by patent law. Likewise, Applicants are not required to recite all that is readily known in the art about stress proteins, nor is it necessary to list all members of a protein family within the claims. What is relevant to definiteness of claim 7 is whether one skilled in the art would be reasonably apprised of what are "members of the hsp70, hsp90, grp78 and grp94 stress protein families". Applicants maintain that, as indicated by the extensive literature cited in the record by both Applicants and the Examiner, those skilled in the art have a clear understanding of the meaning of a stress protein and how stress proteins are categorized into families. Accordingly, Applicants respectfully request that the rejection of claim 7 under 35 U.S.C. §112, second paragraph, be withdrawn.

B. Claim 16

Claim 16 was rejected because the recitation of "associated with" was regarded as rendering the claim vague and indefinite because it is unclear how the claim requires the immunogenic

polypeptide to be associated with a cancer and one of ordinary skill in the art would allegedly not be reasonably apprised of the metes and bounds of the invention.

The recitation of "associated with" is quite common in patent claims and the plain meaning of "associated" is well-understood. Applicants are therefore uncertain as to how this term renders the claim vague and indefinite, nor is it apparent what sort of subject matter would not fall clearly inside our outside the metes and bounds of the claim. One of ordinary skill in the art would readily understand "immunogenic polypeptide associated with a cancer" to refer to a polypeptide that elicits an immune response to a cancer antigen. Accordingly, Applicants have amended claim 16 to replace "wherein the immunogenic polypeptide is associated with a cancer" with "wherein the immunogenic polypeptide comprises a cancer antigen". This amendment to the claim removes any potential ambiguity arising from use of the term "associated with".

C. Claims 33 and 34

Claims 33 and 34 were rejected because the recitation of "an effective amount" was regarded as indefinite when the claims fail to sate the function that is to be achieved. Applicants respectfully note that claims 33 and 34, as originally filed, state that the function to be achieved is "inhibiting tumor growth in the subject" and "inhibiting the development of a cancer in the subject". However, Applicants have amended claims 33 and 34 in accordance with the Examiner's suggestion, by amending these claims to recite "an effective amount of the pharmaceutical composition of claim 16 to elicit an anti-tumor response in the subject".

VI. Prior Art Rejections

A. Rejections Under 35 U.S.C. §102

In paragraph (10) of the Office Action, claims 1, 2, 4-10, 16-18, 23, 33 and 34 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,891,432-A ('432). In paragraph (11) of the Office Action, claims 1-3, 5, 6, 8, 16-18 and 22 were rejected under 35 U.S.C. §102(e) [sic; a rejection under §102(a) and/or (b) may have been intended] as allegedly anticipated by U.S. Patent No. 5,747,332-A ('332). In paragraph (12) of the Office Action, claims 1-3, 5, 6, 8 and 16-18 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,066,716-A ('716). Applicants respectfully traverse these rejections for the reasons provided below.

None of the references cited by the Examiner teaches a pharmaceutical composition comprising a stress protein complex and a physiologically acceptable carrier, wherein the stress protein complex comprises an hsp110 polypeptide and an immunogenic polypeptide. Nor do any of these references teach that such a composition can be used for inhibiting tumor growth in a subject or for inhibiting the development of a cancer in a subject.

To the extent that some earlier-filed patent specifications disclose the use of a heat shock protein in combination with an immunogenic polypeptide, these references do not teach that hsp110 has therapeutic properties. Although hsp110 is mentioned as an example of a heat shock protein, no basis for expecting hsp110 to have the same immunogenic utility as, for example hsp70, is provided. Because one of ordinary skill in the art would not have had a reasonable expectation of success with a pharmaceutical composition comprising hsp110 complexed with an immunogenic polypeptide in the absence of data demonstrating the ability to elicit an effective immune response, none of the cited references provides an enabling disclosure (see MPEP §2121).

Applicants' specification discusses at page 2, lines 23-30, the lack of information available about the function and activity of the larger stress proteins, hsp110 and grp170. This paragraph also points out the divergence of these larger stress proteins from the more extensively studied hsp70 in sequence as well as size. Moreover, the existence of hsp110 in parallel with hsp70 in the cytoplasm, and likewise of grp170 with grp78 in the endoplasmic reticulum is further suggestive of divergent functions. As stated in Applicants' specificaton at page 3, lines 1-2, "[n]ot all stress proteins function as vaccines, however, and it can be expected that different ones may exhibit different activities." This statement that one cannot presume all stress proteins function as vaccines is supported by the specification's disclosure at page 48, lines 7-10, that grp78 failed to exhibit the same immunogenic properties as shown by the other stress proteins studied in this example. Accordingly, the mere fact that hsp110 had been identified as a stress protein was not enough to indicate that it could be used to inhibit cancer or other disease.

1. U.S. Patent 5,891,432 to Hoo ('432)

The '432 patent teaches a vaccine having a membrane-bound fusion protein that includes a non-antibody immunomodulatory molecule fused to a heterologous membrane-attachment domain and further including a disease-associated antigen. Although the specification teaches, and the

claims are directed to, use of GM-CSF as the non-antibody immunomodulatory molecule, the specification also mentions heat shock proteins as an example of a non-antibody immunomodulatory molecule. The paragraph bridging columns 6-7 of '432 lists the various identified families of heat shock proteins: HSP110, HSP90, HSP70, HSP60, HSP25, HSP20 and HSP8.5, and then goes on to note that HSP60, HSP70 and HSP90 are expressed on the cell surface of mycobacteria-infected, HIV-infected, or tumor cells, and that HSP65 is an example of an immunomodulatory molecule useful in the vaccines of the invention. References are cited to support the statements regarding these features of HSP60, HSP70, HSP90 and HSP65. No representation is made, however, that HSP110 shares these same features with HSP60, HSP70, HSP90 and HSP65 or that HSP110 itself would be useful in a vaccine.

Accordingly, the '432 patent does not teach each element of Applicants' claims, and withdrawal of the rejection based on '432 is respectfully requested.

2. *U.S. Patent 5,747,332 to Wallen ('332)*

The '332 patent teaches a method for purifying heat shock proteins. The specification of this patent includes a list of known heat shock proteins, including members of the hsp60 family, the hsp70 family, the hsp90 family and hsp104-105 family, of which hsp110 is identified as a member. The Background portion of this patent, at column 1, lines 39-50, mentions that a number of different heat shock proteins have been shown to exhibit immunogenicity, including gp96, hsp90, and hsp70. The '332 patent does not teach that hsp110 is immunogenic.

Accordingly, the '332 patent does not teach each element of Applicants' claims, and withdrawal of the rejection based on '332 is respectfully requested.

3. *U.S. Patent 6,066,716 to Wallen ('716)*

The '716 patent is a divisional of the '332 patent, and its disclosure is the same as that for the '332 patent. Like the '332 patent, '716 does not teach that hsp110 is immunogenic. Accordingly, the '716 patent does not teach each element of Applicants' claims, and withdrawal of the rejection based on '716 is respectfully requested.

B. Rejections Under 35 U.S.C. §103

In paragraph (14) of the Office Action, claims 1-10, 16-18, 22, 23, 33 and 34 were rejected under 35 U.S.C. §103(a) as allegedly obvious in view of the combination of U.S. Patent Nos. 5,747,332-A ('332), 5,981,706-A ('706), and 6,066,716-A ('716), in view of Disis et al. (Clinical Cancer Research 5:1289-1297, 1999), and further in view of U.S. Patent No. 6,322,790-B1 ('790), and in still further view of U.S. Patent Nos. 5,891,432-A ('432), 6,331,299-B1 ('299), and Lee-Yoon et al. (Journal of Biological Chemistry 270:15725-15733). Applicants respectfully traverse the rejection of these claims for the reasons provided below.

The teachings of '332, '716 and '432 as discussed above, are limited to mentioning the immunogenic properties of some heat shock proteins, namely hsp70, hsp90 and gp96, and the identification that hsp110 is also a heat shock protein. These references do not teach that hsp110 is immunogenic or otherwise useful in the inhibition of cancer. Prior to Applicants' invention, it was not known that hsp110 has immunogenic properties and is suitable for use as a vaccine (see publication by the inventors: Wang et al., 2001, J. Immunology 165:490-497). The 5 additional references on which the rejection under 35 U.S.C. §103 is based are discussed below.

1. U.S. Patent 5,981,706 to Wallen ('706)

The '706 is a continuation-in-part of the '332 patent, and its disclosure includes that for the '332 patent plus adds a number of specific examples of peptides for use in ADP-heat shock protein-peptide complexes. Like the '332 patent, '706 does not teach that hsp110 is immunogenic. It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

Moreover, '706 teaches the purification of heat shock proteins through complexing with ADP. Because hsp110 does not bind ATP or ADP, hsp110 could not be used in the manner taught in '706. The same teaching that hsps are purified by complexing with ADP is found in the remaining Wallen patents ('332 and '716 above). Accordingly, all of the Wallen patent teach away from the use of hsp110.

2. *Disis et al., Clinical Cancer Research 5:1289-1297, 1999 (Disis)*

Disis teaches that immunity to the her2/neu oncogenic protein can be generated in patients with breast or ovarian cancer using peptides derived from the her2/neu protein. It does not teach or suggest combining an immunogenic her2/neu peptide with hsp110. It does not teach or suggest the use of hsp110 to inhibit cancer.

3. *U.S. Patent 6,322,790 to Srivastava ('790)*

The '790 patent teaches stress proteins complexed with peptides and their use for eliciting an immune response. It mentions hsp70, hsp90 and gp96 as examples of stress proteins that have demonstrated ability to elicit an immune response (column 3, lines 23-51). It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

4. *U.S. Patent 6,331,299 to Rothman ('299)*

The '299 patent teaches use of polynucleotides encoding a heat shock protein to elicit an immune response. It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

5. *Lee-Yoon et al., J. Biol. Chem. 270:15725-15733, 1995 (Lee-Yoon)*

Lee-Yoon teaches that the amino acid sequence for hamster hsp110 shares about 30-33% identity with members of the hsp70 family, and that hsp110 is a large and highly unusual heat shock protein that diverges considerably from the hsp70 family. At page 15732, Lee-Yoon discusses the potential functions of hsp110 based on the deduced amino acid sequence of this protein, and concludes that hsp110 may be expected to show both similarities and differences in function with respect to the more extensively studied hsp70. It does not teach or suggest the use of hsp110 to inhibit cancer or to elicit an immune response.

6. *The 8 References Do Not Teach or Suggest the Claimed Invention*

Because none of the 8 references cited in the Office Action teaches that hsp110 is capable of eliciting an immune response, these references cannot teach or suggest a pharmaceutical

composition comprising hsp110 and an immunogenic polypeptide nor can they teach or suggest use of such a composition for inhibiting cancer or tumor growth. Even when combined, the references teach away from Applicants' invention. For example, the combined references would teach use of a pharmaceutical composition comprising a heat shock protein selected from hsp70, hsp90 or gp96, and would lead the skilled artisan away from the use of hsp110.

VII. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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APPENDIX: CLAIMS IN MARKED-UP FORM

1. (Amended) A pharmaceutical composition comprising a stress protein complex and a physiologically acceptable carrier, wherein the stress protein complex comprises an hsp110 [or grp170] polypeptide and an immunogenic polypeptide.

2. (Amended) The pharmaceutical composition of claim 1, wherein the hsp110 [or grp170] polypeptide is complexed with the immunogenic polypeptide.

3. (Amended) The pharmaceutical composition of claim 2, wherein the hsp110 [or grp170] polypeptide is complexed with the immunogenic polypeptide by non-covalent interaction.

9. (Amended) A pharmaceutical composition comprising a first polynucleotide encoding an hsp110 [or a grp170] polypeptide and a second polynucleotide encoding an immunogenic polypeptide.

16. (Amended) The pharmaceutical composition of claim 1, wherein the immunogenic polypeptide [is associated with] comprises a cancer antigen.

19. (Amended) The pharmaceutical composition of claim [1, wherein the immunogenic polypeptide is associated with an infectious disease] 17, wherein the her-2/neu peptide is derived from the extracellular domain of her-2/neu.

20. (Amended) The pharmaceutical composition of claim [19, wherein the immunogenic polypeptide comprises a *M. tuberculosis* antigen] 17, wherein the her-2/neu peptide is derived from the transmembrane region of her-2/neu.

21. (Amended) The pharmaceutical composition of claim [20, wherein the *M. tuberculosis* antigen is Mtb8.4 or Mtb39] 16, wherein the cancer is colon cancer.

22. (Amended) The pharmaceutical composition of claim 1, wherein the complex has been heated so as to enhance binding of the hsp110 [or grp170] polypeptide to the immunogenic polypeptide.

33. (Amended) A method for inhibiting tumor growth in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 16 to elicit an anti-tumor immune response in the subject, and thereby inhibiting tumor growth in the subject.

34. (Amended) A method for inhibiting the development of a cancer in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 16 to elicit an anti-tumor immune response in the subject, and thereby inhibiting the development of a cancer in the subject.